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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,371	04/08/2002	Gregor Cevc	NTP 1931	1865

85965 7590 10/27/2009

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
10/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/890,371	CEVC ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-63,65-103 and 105-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-63,65-103 and 105-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/17/09, 7/27/09, 7/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Applicant's response to the office action mailed on 12/11/2008, including arguments/remarks and amended claims, was received on 5/11/2009 and has been entered into the record. Additionally, the supplemental response received on 7/17/2009 has also been made of record.

2. In the response received on 5/11/2009, the Applicants added new claims 105-114. Therefore, claims 54-63, 65-103, and 105-114 are pending and are the subject of this office action.

Information Disclosure Statement

The information disclosure statements received on 7/17/2009, 7/27/2009, and 7/30/2009 have been fully considered.

Rejections Withdrawn

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 54-63 and 65-103 under 35 USC § 112, first paragraph, regarding lack of enablement for methods of transnasally administering a composition comprising any two substances other than soybean phosphatidylcholine and either Tween 80 or sodium cholate, as set forth on pages 2-4 of the office action mailed on 12/11/2008, is *withdrawn*.

In the response received on 5/11/2009, as well as the supplemental response received on 7/13/2009, the Applicants argue that the prior art, and Santus *et al* (US 6,333,044) teach unpredictability regarding nasal administration of various active ingredients, wherein this nasal administration involves

"adsorption" or "permeation" of the active ingredient through the nasal mucosa. In contrast, the Applicants note that the claimed penetrant compositions facilitate drug delivery through pre-existing pores in the nasal mucosa. Specifically, because the claimed penetrants are deformable, they do not spread irritants such as surfactants/bile salts all over the mucosa in the same manner as state of the art absorption techniques, and therefore do not promote destruction and/or irritation of the nasal mucosa. The Applicants also note that the specification disclosed no irritation resulting from administration of various penetrant formulations.

Furthermore, the Applicants argue that the claimed penetrant formulations are useful for administering numerous active ingredients. Specifically, the Applicants note that Santus et al describes nasal administration of 9 different substances, while the specification exemplifies nasal administration of 11 additional substances. Furthermore, the Applicants assert that the specification teaches that the present invention allows for administration of different size molecules while preserving their biological activities, including higher molecular weight molecules which were previously considered to be difficult to administer transnasally. For these reasons, the Applicants argue that the specification is enabling for methods of transnasally administering various active ingredients using the claimed penetrant formulations.

These arguments have been fully considered and are persuasive.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejection of claims 54-63 and 65-103 under 35 USC § 112, first paragraph, regarding lack of written description for the genus of active ingredients which can be transnasally administered, and the genus of phospholipids and surfactants which can be used without provoking undesirable side effects, as set forth on pages 5-6 of the office action mailed on 12/11/2008, is *withdrawn*.

In the response received on 5/11/2009, as well as the supplemental response received on 7/13/2009, the Applicants argued that the specification provides numerous examples of active substances which can be transnasally administered using the claimed invention (as discussed above), and additionally, the art (Santus *et al*) also provides a listing of substances which can be transnasally administered. As such, the genus of active substances which can be transnasally administered by the claimed method has been adequately described.

Regarding the genus of phospholipids and surfactants that can be used to practice the claimed method, the Applicants argue that the specification provides adequate written description by providing a

listing of exemplary phospholipids and surfactants, as well as specific examples of penetrant formulations, which can be used in the claimed method. Additionally, the Applicants assert that the claimed penetrants deliver active ingredients across the nasal membrane via penetration, rather than permeation/absorption, using pre-existing pores in the nasal mucosa and thus do not cause excessive irritation or mucosa damage as is commonly seen in other methods of transnasal administration using permeation/absorption. For these reasons, the Applicants argue that the genus of phospholipids and surfactants that can be used in the claimed invention have been adequately described.

These arguments have been fully considered and are persuasive.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the phrase “wherein the at least two substances are two forms of a substance”. It is not clear how two substances can be one substance, even in two forms. Are there two substances, or are there two forms of one substance?

2. Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the phrase “the active ingredient are associated with the penetrant”. It is not clear what is meant by “associated with the penetrant”. Is the active ingredient contained within the penetrant, attached somehow, or in solution with the penetrant?

3. Claims 93, 102, and 105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite an antigen that is “derived” from a pathogen, and a ”derivative” of a peptide, polypeptide, or protein. It is not clear what the term "derived from" is intended

to mean. Furthermore, it is not clear what is encompassed by a "derivative" of a peptide, polypeptide, or protein.

4. Claims 59, 96, and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite various acronyms, such as IL-4, IL-3, GM-CSF, MPL, etc, that have not been defined upon the first use in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 54-59, 61-63, 65-87, 89-93, 97-103, and 105-114 are rejected under 35 U.S.C. 103(a) as being obvious over Cevc *et al* ("Cevc" – *Biochem. Biophys. Acta*., Jan 19, 1998, Vol. 1368(2), p. 201-215 – cited in the IDS received on 10/23/03), and Modi *et al* ("Modi" - US 5,653,987).

Cevc discloses a pharmaceutical preparation for delivering insulin across the skin, wherein said preparation comprises insulin as the active ingredient, and further comprises soybean phosphatidylcholine and sodium cholate (see p. 203, section 2.5), and therefore teaches a composition comprising an active ingredient and two substances which are identified by the specification as a phospholipid (phosphatidylcholine) and a surfactant (sodium cholate) which differ by a factor of 10 in terms of solubility. Thus, in the absence of evidence to the contrary, the composition of Cevc would be expected to meet the structural/composition limitations recited in claims 54 and 100 of the present application. Cevc is silent regarding transnasal administration of this preparation.

However, Modi discloses formulations for nasal delivery of various active ingredients. Specifically, Modi teaches formulations which are suitable for nasal administration comprising an active ingredient and at least two absorption enhancing compounds, which can include sodium deoxycholate or Tween 80, and phospholipids (column 2, lines 12-65). Specific phospholipids are taught to be phosphatidylcholine and phosphatidylethanolamine (column 3, lines 1-4). Modi also discloses numerous

active ingredients that can be nasally administered using such compounds, including cytokines such as IL-2, insulin, heparin, various vaccine for infectious organisms (mumps, measles, rubella, typhoid, bacterial toxins, and cholera toxin (see claim 9).

Therefore, a person of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to practice a method of transnasal administration of active ingredients using the claimed compositions/formulations. The motivation to do so comes from Cevc, which teaches transdermal administration of a formulation which meets the limitations of the formulations of the instant claims, and Modi, which teach phosphatidylcholine and sodium deoxycholate are useful for enhancing nasal administration of various substances.

In the office action mailed on 10/10/2007, a similar rejection was withdrawn in view of the 1.132 declaration by Dr. Cevc, which stated that the Cevc references teaches away from transnasal administration due to the lack of an effective water gradient across the nasal membranes, and that the fact that the present formulations were effective for nasal administration was thus completely unexpected. The difference between this rejection and the previously withdrawn rejection is the teachings of Modi. A person of ordinary skill in the art, in following the teachings of Modi, would know that phosphatidylcholine and sodium deoxycholate or Tween 80 are useful for promoting nasal administration of various substances, and for this reason a person of ordinary skill in the art would expect that the formulation of Cevc would be effective for nasal administration. Therefore, regardless of the mechanism by which the formulation functions (penetration vs absorption/permeation), a person of ordinary skill in the art would be motivated to practice methods of transnasal administration using Cevc's formulation because Modi teaches that formulations comprisng phosphatidylcholine and sodium deoxycholate are suitable for nasal administration.

Furthermore, although neither Cevc nor Modi specifically disclose each specific structural limitation of the present claims (such as the specific diameter of the droplets, deformation energy of the droplets, etc), it is noted that because the formulation of Cevc is the same as that claimed and also exemplified in the specification, the formulation of Cevc would inherently possess these characteristics. Similarly, while neither Cevc nor Modi specifically teach the specific concentrations of penetrants within the claimed pharmaceutical compositions, pH of the compositions, and active ingredient concentrations, a person of ordinary skill in the art would have both the motivation and the ability to optimize such variables. MPEP 2144.05 states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, the combination of Cevc and Modi provide the motivation to practice the general conditions of the claims, namely that of transnasal administration of various active ingredients in a formulation comprising two substances (phosphatidylcholine and either sodium deoxycholate or Tween 80) which differ in solubility by a factor of at least 10. Thus, the optimization of pH, active ingredient concentration, etc, would not be inventive but would instead constitute routine optimization.

2. Claim 60 is rejected under 35 U.S.C. 103(a) as being obvious over Cevc *et al* ("Cevc" – *Biochem. Biophys. Acta*., Jan 19, 1998, Vol. 1368(2), p. 201-), in view of Modi *et al* ("Modi" - US 5,653,987), and further in view of Levitt *et al* (US 6,261,559).

Claim 60 of the present invention is drawn to the claimed method of transnasally administering an active ingredient, wherein said active ingredient is an anti-cytokine antibody or active fragment thereof. The teachings of Cevc and Modi are discussed above; neither teach administration of an anti-cytokine antibody or an active fragment thereof.

However, Levitt teaches administration of anti-interleukin-– (IL-9) antibodies for treatment of a variety of disorders, including asthma and atopic allergies. Levitt teaches inhalation of anti-IL-9 antibodies (see claims 12-13) and also teaches systemic and topical administration of anti-IL-9 antibodies.

A person of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to practice the method of claim 60 by following the combined teachings of Cevc, Modi, and Levitt because Levitt teaches that systemic or topical anti-IL-9 antibody administration is useful for treating various diseases, and Cevc and Modi such a method of administration. Therefore, a skilled artisan would know that the anti-IL-9 antibodies of Levitt could be administered via the method of transnasal administration suggested by the combination of Cevc and Modi.

3. Claim 88 is rejected under 35 U.S.C. 103(a) as being obvious over Cevc *et al* ("Cevc" – *Biochem. Biophys. Acta*., Jan 19, 1998, Vol. 1368(2), p. 201-), in view of Modi *et al* ("Modi" - US 5,653,987), and further in view of Grayson *et al* (US 4,095,596).

Claim 88 of the present invention is drawn to the claimed method of transnasally administering an active ingredient, wherein the formulation is administered using a metered delivery device. The teachings of Cevc and Modi are discussed above; neither teach nasal administration using a metered dose device.

However, Grayson discloses a nasal inhalation device which delivers a dosage of various substances to the nasal mucosa, and thus could be considered to be a metered delivery device.

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to use the nasal inhalation device of Grayson to nasally administer the formulations of the present invention which are obvious in view of Cevc and Modi, as discussed above. The motivation to do so comes from Cevc and Modi, which teach and/or suggest formulations for nasal administration, and Grayson, which provides a specific, metered delivery device capable of such administration.

4. Claims 94-95 are rejected under 35 U.S.C. 103(a) as being obvious over Cevc *et al* ("Cevc" – *Biochem. Biophys. Acta*., Jan 19, 1998, Vol. 1368(2), p. 201-), in view of Modi *et al* ("Modi" - US 5,653,987), and further in view of Adam *et al* (US 4,036,953).

Claim of 94-95 the present invention are drawn to the claimed method of transnasally administering a vaccine and an adjuvant, wherein said adjuvant is an extract of a microorganism. The teachings of Cevc and Modi are discussed above; neither teach transnasal administration of a vaccine with an adjuvant, and specifically an adjuvant that is an extract of a microorganism.

However, Adam teaches preparation of vaccine adjuvants for enhancement of immune responses to vaccines, wherein said adjuvants comprise a suspension of Mycobacteria or Nocardia cell wall components.

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to practice the claimed method of transnasally administering a vaccine antigen and an adjuvant which is an extract of a microorganism. The motivation to do so comes from the combined teachings of Cevc and Modi, which suggest transnasal administration of various active ingredients, including different vaccine antigens, using the formulations of the present invention as discussed above. Further motivation is provided by Adam, which shows that the response to a vaccine antigen can be enhanced by an adjuvant comprising a Mycobacterial extract of cell wall material. Thus, a person of ordinary skill in the art would be motivated to formulate the Mycobacterial cell wall extract adjuvant of Adam with the nasal formulations comprising vaccines suggested by Cevc and Modi because the skilled artisan would know that such vaccines can be nasally administered, and co-administration with the adjuvant of Adam would further enhance the effectiveness of the vaccine formulation.

5. Claims 94 and 96 are rejected under 35 U.S.C. 103(a) as being obvious over Cevc *et al* ("Cevc" – *Biochem. Biophys. Acta*., Jan 19, 1998, Vol. 1368(2), p. 201-), in view of Modi *et al* ("Modi" -

US 5,653,987), and further in view of Schwartz (Allergy, 1995, Vol. 50, p. 292-302 – cited in the IDS received on 10/30/06).

Claims 94 and 96 of the present invention are drawn to the claimed method of transnasally administering a vaccine and an adjuvant, and further comprising administration of IL-4 and GM-CSF. The teachings of Cevc and Modi are discussed above; neither teach co-administration with IL-4 and GM-CSF.

However, Schwartz teaches that IL-4 is a cytokine which stimulates B cell development and secretion of IgG1 and IgE antibodies by B cells (see p. 295), while GM-CSF promotes antigen presentation by Langerhans cells within the skin

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to practice the claimed method of transnasally administering a vaccine antigen and IL-4 and GM-CSF. The motivation to do so comes from the combined teachings of Cevc and Modi, which suggest transnasal administration of various active ingredients, including different vaccine antigens, using the formulations of the present invention as discussed above. Further motivation is provided by Schwartz, which shows that IL-4 promotes B cell development and antibody production, which GM-CSF enhances antigen presentation. Because a person of ordinary skill in the art would readily understand that enhancement of these activities would be important for enhancing the response to a vaccine, the skilled artisan would also be motivated to co-administer IL-4 and GM-CSF with the claimed transnasal formulations for the purpose of enhancing an immune response against said vaccine antigent.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
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/Robert Landsman/
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